*Acta Med. Nagasaki* 66: 29－34

# Fluid collection and pancreatic fistula after pancreaticoduodenectomy

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**Background:** Although postoperative abdominal fluid collection (POFC) is an important predictive factor for clinically relevant postoperative pancreatic fistula (CR-POPF), many patients are asymptomatic and resolve spontaneously. Triple-drug therapy consisting of gabexate mesylate, octreotide, and carbapenem antibiotics has been used at our institution to prevent pancreatic fistula after pancreatectomy. The present study aimed to evaluate the management and outcomes of patients with POFC and to determine the efficacy of triple-drug therapy to prevent CR-POPF after pancreaticoduodenectomy (PD).

**Methods:** From 2016 to 2021, 125 patients who underwent PD were retrospectively analyzed to determine their postoperative fluid collection status. Triple-drug therapy was administered to patients who showed high amylase levels in their drainage (> 10,000 IU/L) on POD 1, 3, or 5, and who had any clinical symptoms associated with POFC.

**Results:** The overall rate of POFC was 26% (n=33). Among these patients, CR-POPF developed in 16 patients (48%). There was no CR-POPF patient in the NO-POFC patient group. Triple-drug therapy was performed for 30 patients according to a preexisting treatment algorithm. Among these 30 patients, there were 23 POFC and 7 No-POFC patients. Twelve (52%) of the POFC patients developed CR-POPF despite treatment with triple-drug therapy. There were no CR-POPF patients in the No-POFC patient group.

**Conclusions:** Although POFC after PD is an important finding for CR-POPF, it does not necessarily develop into CR-POPF. The administration of triple-drug therapy is effective for the prevention of CR-POPF in cases without POFC fluid drainage as well as in those with POFC.

ACTA MEDICA NAGASAKIENSIA 66: 29－34, 2022

**Key words:** Fluid collection, pancreatic fistula, pancreaticoduodenectomy, triple-drug therapy.

## Introduction

Postoperative pancreatic fistula (POPF) is the most important complication after pancreatic surgery and can sometimes be fatal. The International Study Group of Pancreatic Surgery (ISGPS) provides simple criteria and a universally applicable definition for POPF[1]. According to the 2016 update of the ISGPS definition, a grade-A POPF has been redefined as a "biochemical leak", as it has no clinical effect. On the other hand, grade B and C POPF are regarded as clinically relevant POPF (CR-POPF), requiring changes in postoperative management including percutaneous or endoscopic drainage, frequent radiological management, and additional therapeutic antibiotics or somatostatin analog, and reoperation. For postoperative imaging, computed tomography (CT) has been reported as useful for the detection of the postoperative abdominal fluid collection (POFC) associated with POPF after pancreatectomy[2-4]. However, not all POFC is associated with CR-POPF. In other words, patients with POFC may not require invasive treatment but rather, only follow-up or preventive measures against CR-POPF[5].

CR-POPF can lead to life-threatening complications such as sepsis, intra-abdominal abscess, and massive hemorrhage due to the rupture of a pseudoaneurysm[6]. Adachi et al. reported

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Received March 30, 2022; Accepted May 19, 2022

that the original triple-drug therapy, namely, gabexate mesylate, octreotide, and carbapenem antibiotics, prevented CR-POPF after pancreatectomy[7,8]. Therefore, the present study aimed to evaluate the management and outcomes of patients with POFC and to determine the efficacy of triple-drug therapy to prevent CR-POPF after pancreaticoduodenectomy (PD).

## Materials and methods

### *Patients*

This retrospective analysis was undertaken on 125 consecutive patients undergoing PD at the National Hospital Organization Nagasaki Medical Center between April 2016 and December 2021. The clinical characteristics, operative variables, and postoperative outcomes of patients with and without POFC were retrospectively analyzed. Informed consent was obtained from all patients, and the study protocol was approved by the Ethics Committee of the National Hospital Organization Nagasaki Medical Center.

### *Operative technique*

All PDs were performed by expert pancreatic surgeons. A modified Child reconstruction method with subtotal stomach-preserving PD was the standard procedure for PD. Pancreatic reconstruction was performed using a duct-to-mucosa anastomosis for pancreatojejunostomy or invaginated anastomosis for pancreaticogastrostomy, based on surgeon preference. In patients with malignant disease, lymphadenectomy was routinely performed with skeletonization at the hepatoduodenal ligament. Two closed-suction drainage tubes were routinely placed at the pancreatic anastomosis, one from the right side of the patient via the foramen of Winslow and the other straight from the left side of the patient.

### *Postoperative management*

Cephem-based prophylactic antibiotics were administered for three days including the day of surgery. All patients were admitted to the intensive-care unit on the day of surgery. On postoperative days (POD) 1, 3, and 5, routine blood analysis was performed, and amylase levels of both drains were measured. Typically, both drains were removed on POD 5. If the purulent discharge was detected in the drain, drainage management was continued. Postoperative CT and/or ultrasound examinations were performed for the evaluation of POFC. Postoperative CT or US was not routinely performed on a fixed POD. In the majority of patients, postoperative CT or US were performed around POD 7.

Triple-drug therapy consisting of gabexate mesylate (600 mg/day as a continuous intravenous injection), octreotide (300 μg/day continuous intravenous injection), and carbapenem antibiotics (0.5 g/day intravenous injections) was administered to patients who showed high amylase levels (> 10,000 IU/L) in the drainage fluid on POD 1, 3 or 5, and who had any clinical symptoms with POFC despite low amylase level of the drain, according to the method previously described by Adachi et al[7]. Triple-drug therapy was administered for 7 days. If the patient's condition had not improved, additional treatment including drain reinsertion, percutaneous abscess drainage, or re-laparotomy was performed.

### *Definition of POFC and CR-POPF*

POFC was defined as a massive fluid collection around the remnant pancreas detected by postoperative CT and/or ultrasound examination. POPF was classified according to the method described by Bassi et al., and Grade B/C POPF was defined as CR-POPF[1].

### *Data collection and statistical analysis*

The preoperative clinical status was examined of age, gender, body mass index (BMI), percentage of invasive malignant tumor, percentage of diabetes mellitus, percentage of soft pancreas texture (evaluation of the operating surgeon), the diameter of the main pancreatic duct, percentage of pancreatic-jejunal anastomosis, operative time, blood loss, percentage of blood transfusion. Outcomes were examined regarding postoperative drain amylase levels, WBC, and CRP on POD1, 3, and 5. The high amylase level in the two drains was used for comparison.

Variables are described as either absolute numbers or median values and ranges. The Mann-Whitney *U*-test and Fisher's exact test were used for comparative evaluations between the two groups. The utility of the predictors was ascertained using sensitivity and specificity calculations and receiver-operating characteristic (ROC) analyses. $p < 0.05$ was considered statistically significant.

## Results

The overall rate of POFC was 26% (n=33). Among the POFC patients, CR-POPF occurred in 16 patients (48%), and all 16 patients showed grade B CR-POPF. On the other hand,

there was no CR-POPF patient in the No-POFC patient group (Figure 1).

Clinical characteristics and perioperative variables of POFC and No-POFC patient groups are shown in Table 1. The percentage of the invasive malignant tumor was significantly lower in the POFC group than in the No-POFC group ($p$=0.044). In addition, there were significant differences between the two groups in variables of the soft pancreas rate ($p$<0.001) and the diameter of the main pancreatic duct ($p$=0.001). There were no significant differences in age, gender, BMI, diabetes mellitus rate, pancreatic-jejunal anastomosis rate, operative time, blood loss, or blood transfusion rate between POFC and No-POPC groups. Comparisons of drain amylase levels, WBCs, and CRP values of 125 patients with or without POFC are shown in Table 2. Drain amylase levels on POD 1, 3, and 5 were significantly higher in the POFC group than in the No-POFC group. In addition, there were significant differences in WBC on POD 5, and in CRP on

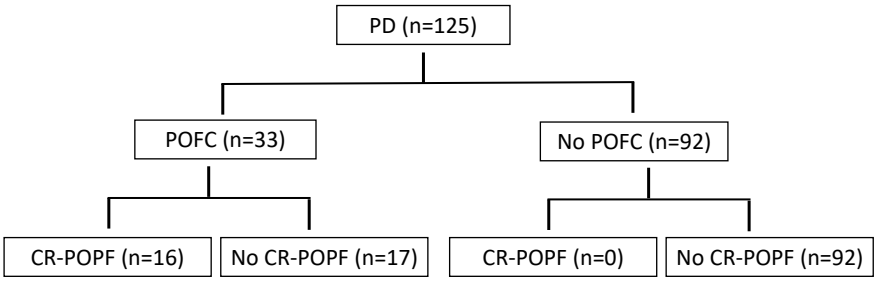


**Figure 1.** The patient flow chart in the study. PD, pancreaticoduodenectomy; POFC, postoperative abdominal fluid collection; CR-POPF, clinically relevant postoperative pancreatic fistula.

**Table 1.** Clinical characteristics and perioprative variables of 125 patients with versus without POFC

| Variable | POFC (n=33) | No POFC (n=92) | P value |
|---|---|---|---|
| Age [years] (median, range) | 70 (37-87) | 71.5 (42-84) | 0.550 |
| Gender (male/female) | 21/12 | 61/31 | 0.832 |
| BMI (median, range) | 21.51 (13.33-33.75) | 20.54(12.82-32.00) | 0.112 |
| Invasive malignant tumor (%) | 24 (73%) | 82 (89%) | 0.044 |
| Diabetes mellitus (%) | 4 (12%) | 24 (26%) | 0.144 |
| Soft pancreatic texture (%) | 31 (94%) | 52 (57%) | <0.001 |
| Diameter of main pancreatic duct [mm] (median, range) | 3 (1-6) | 4 (1-15) | 0.001 |
| Pancreato-jejunal anastomosis (%) | 24 (73%) | 73 (79%) | 0.470 |
| Operative time (median, range) | 345 (227-517) | 344 (236-567) | 0.960 |
| Blood loss (median, range) | 525 (40-1590) | 507.5 (45-4106) | 0.475 |
| Blood transfusion (%) | 2 (6%) | 17 (17%) | 0.151 |

**Table 2.** Comparisons on drain amylase level, WBC, and CRP of 125 patients with versus without POFC

| Variable | POFC (n=33) | No POFC (n=92) | P value |
|---|---|---|---|
| Drain amylase level [IU/L] (median, range) | | | |
| POD1 | 7,755 (372-72,353) | 993 (13-62,579) | <0.001 |
| POD3 | 1,143 (48-9,957) | 130 (8-4,302) | <0.001 |
| POD5 | 325 (31-11,589) | 36 (5-26,570) | <0.001 |
| WBC [count/μL] (median, range) | | | |
| POD1 | 12,600 (3,300-31,700) | 11,350 (3,000-20,700) | 0.381 |
| POD3 | 9,700 (3,300-21,000) | 8,200 (2,700-20,600) | 0.328 |
| POD5 | 8,500 (2,300-19,000) | 6,700 (1,500-17,100) | 0.005 |
| CRP [mg/dl] (median, range) | | | |
| POD1 | 9.46 (4.99-27.91) | 8.05 (3.71-20.79) | 0.102 |
| POD3 | 22.15 (9.14-35.79) | 11.46 (3.14-48.82) | <0.001 |
| POD5 | 17.17 (3.01-28.46) | 6.43 (0.58-26.11) | <0.001 |

POD 3 and 5. Table 3 shows the clinical characteristics and perioperative variables of the 33 POFC patients divided into those with and without CR-POPF. There were no significant differences between groups in the age, gender, BMI, invasive malignant tumor rate, diabetes mellitus rate, soft pancreas texture rate, diameter of main pancreatic duct, pancreatic-jejunal anastomosis rate, operative time, blood loss, or blood transfusion rate. Table 4 shows a comparison of the drain amylase levels, WBCs, and CRP values of the 33 POFC patients with and without CR-POPF. Only the drain amylase level on POD 1 was significantly higher in the group with CR-POPF than in that without ($p$=0.004). ROC analysis was performed to determine an accurate cut-off value of the drain amylase level on POD 1 to be used as a predictive factor for CR-POPF in the POFC patients. The area under the ROC curve was 0.765 (95% confidence interval: 0.598-0.932) with a calculated optimal cut-off value of 7010 U/L (Figure 2).

Triple-drug therapy was performed on 30 patients according to our algorithm. Of these 30 patients, there were 23 POFC and 7 No-POFC patients. Twelve (52%) of the POFC patients developed CR-POPF despite treatment with triple-drug therapy. On the other hand, there was no CR-POPF patient in the No-POFC patient group. In the POFC patients group, CR-POPF occurred in 4 patients without triple-drug therapy (Figure 3).

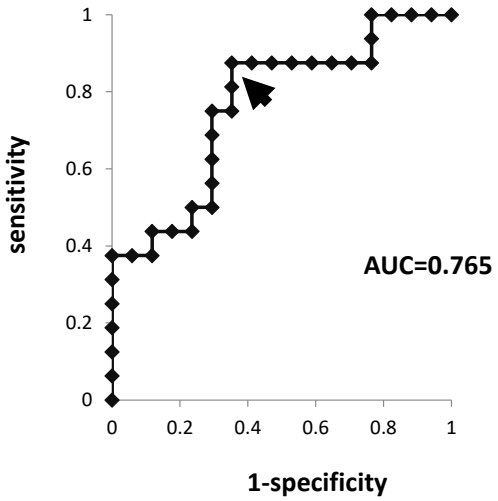


**Figure 2.** ROC curve of drain amylase level on POD 1for rates of CR-POPF in POFC patients. CR-POPF, clinically relevant postoperative pancreatic fistula; POFC, postoperative abdominal fluid collection.

**Table 3.** Clinical characteristics and perioprative variables of 33 POFC patients with versus without CR-POPF

| Variable | CR-POPF (n=16) | No CR-POPF (n=17) | P value |
|---|---|---|---|
| Age [years] (median, range) | 69.5 (37-87) | 70 (50-85) | 0.787 |
| Gender (male/female) | 9/7 | 12/5 | 0.481 |
| BMI (median, range) | 20.65 (18.39-25.85) | 21.65(13.33-33.75) | 0.692 |
| Invasive malignant tumor (%) | 12 (75%) | 12 (71%) | 1.000 |
| Diabetes mellitus (%) | 2 (13%) | 2 (12%) | 1.000 |
| Soft pancreatic texture (%) | 16 (100%) | 15 (88%) | 0.485 |
| Diameter of main pancreatic duct [mm] (median, range) | 3 (1-6) | 3 (1-6) | 0.837 |
| Pancreato-jejunal anastomosis (%) | 11 (69%) | 13 (76%) | 0.708 |
| Operative time (median, range) | 344.5 (227-462) | 347 (232-517) | 0.986 |
| Blood loss (median, range) | 462.5 (40-1535) | 525 (75-1590) | 0.368 |
| Blood transfusion (%) | 1 (6%) | 1 (6%) | 1.000 |

**Table 4.** Comparisons on drain amylase level, WBC, and CRP of 33 POFC patients with versus without CR-POPF

| Variable | CR-POPF (n=16) | No CR-POPF (n=17) | P value |
|---|---|---|---|
| Drain amylase level [IU/L] (median, range) | | | |
| POD1 | 11,077 (2593-72,353) | 6,258 (372-13,657) | 0.004 |
| POD3 | 717 (48-9,957) | 1,239 (57-5,272) | 0.773 |
| POD5 | 357 (47-11,589) | 315 (31-2,033) | 0.589 |
| WBC [count/μL] (median, range) | | | |
| POD1 | 12,650 (5,500-31,700) | 11,400 (3,300-17,500) | 0.957 |
| POD3 | 9,700 (4,300-21,000) | 9,700 (3,300-14,800) | 0.652 |
| POD5 | 8,600 (3,600-19,000) | 8,500 (2,300-14,300) | 0.528 |
| CRP [mg/dl] (median, range) | | | |
| POD1 | 9.70 (6.24-14.70) | 9.39 (4.99-27.91) | 0.102 |
| POD3 | 22.15 (13.59-35.71) | 22.36 (9.14-35.79) | 0.453 |
| POD5 | 18.50 (8.63-28.46) | 14.82 (3.01-27.63) | 0.150 |

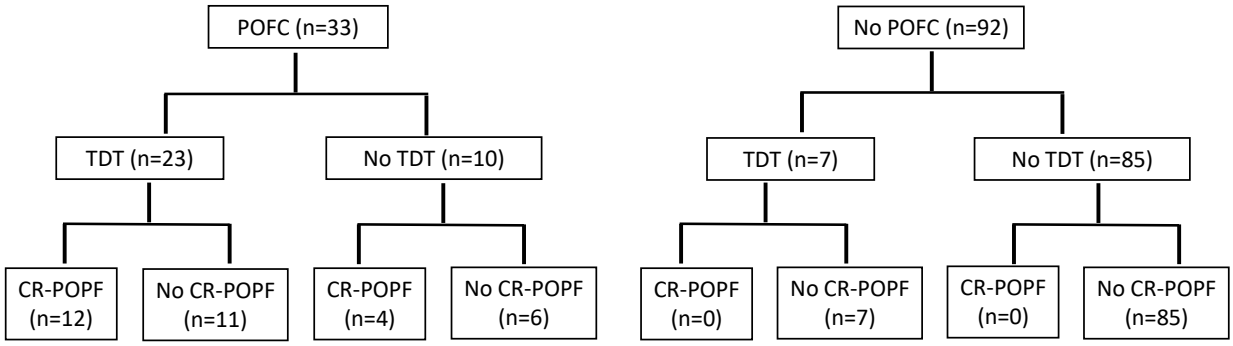


**Figure 3.** Patient flow chart of TDT. TDT, triple-drug therapy; POFC, postoperative abdominal fluid collection; CR-POPF, clinically relevant postoperative pancreatic fistula.

## Discussion

POFC is one of the most important findings following PD because it can be a sign of fatal complications such as pancreatic fistula, bile leakage, intra-abdominal abscess, and/or hemorrhage[9,10]. The present study demonstrated that POFC is an important factor in the development of CR-POPF after PD. However, 52% (17/33) of the cases of POFC did not develop CR-POPF. Sierzega et al.[5] reported that 65% (97/149) of patients with the abdominal fluid collection were asymptomatic and resolved spontaneously while POPF was detected in 13% (20/149). Among the No-POFC patient group, 7 were treated with triple-drug therapy, and none of these 7 patients developed CR-POPF. Therefore, if there is no POFC, the occurrence of CR-POPF can be suppressed by performing triple-drug therapy. On the other hand, 4 patients were not indicated triple-drug therapy and developed CR-POPF without receiving triple-drug therapy in the POFC group. Therefore, it may be necessary to reconsider our indication criteria for the administration of triple-drug therapy. The present study demonstrated that the drain amylase level on POD 1 was a significant predictive factor of CR-POPF in the group of POFC after PD. In addition, our cut-off value of the drain amylase level on POD 1 was 7010 U/L by ROC analysis. Several reports demonstrated the cut-off value of the drain amylase level as a predictor of CR-POPF after pancreatectomy. Fukami et al.[11] reported a cut-off level of 1757 U/L on POD 1 for the drain amylase. Trudeau et al. proposed a value of 5000 U/L on POD 1 for the prediction of CR-POPF after PD. Noji et al.[12] reported a cut-off of 3000 U/L on POD 3 and found that the POD 3 drain amylase level was more useful than that of POD 1 for the prediction of CR-POPF after pancreatic-enteral anastomosis. These findings suggest that, for the prediction of CR-POPF, the optimal cut-off for the drain amylase level and the optimal POD day for its measurement are uncertain.

Several risk factors for CR-POPF have been reported, including the texture of the remnant pancreatic parenchyma[13-15]. Our present study demonstrated that a soft pancreatic texture was one of the most important predictive factors for POFC. In addition, all CR-POPF cases showed POFC after PD. Therefore, POFC in cases with soft pancreatic texture is likely to develop CR-POPF after PD. A small pancreatic duct diameter was another important risk factor for CR-POPF. The diameter of the main pancreatic duct can be evaluated preoperatively, and therefore has a different utility than the pancreatic texture evaluated intraoperatively.

The main limitations of this study were the relatively small number of subjects, the fact that they were drawn from a single-center, and the retrospective nature of the study. In addition, the definition of POFC after PD is unclear. However, it seems very significant that the effectiveness of triple-drug therapy for the prevention of CR-POPF after PD has been confirmed at our facility. A large prospective multicenter study with a very specific definition of POFC should be performed in the future.

In conclusion, our present study demonstrated that although POFC after PD is an important finding for CR-POPF, cases with POFC do not necessarily develop into CR-POPF. The administration of triple-drug therapy is effective for the prevention of CR-POPF, in cases both with and without POFC.

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